APPENDIX 4

PATENT CORPORATE BODY

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

U.S. Patent Application No. 10/561,629
(U.S. National Phase of PCT/JP2004/008710)
Of Yuka MATSUI (KOBAYASHI PHARMACEUTICAL CO., LTD.)

I, **Seung-Lim SUNG**, of ARCO PATENT OFFICE at 3rd Fl., Bo-eki Building, 123 Higashi-machi, Chuo-ku, Kobe 650-0031 JAPAN, declare that I am familiar with the Japanese and the English languages, and, to the best of my knowledge and belief, the attached is full, true, complete and faithful my prepared English translation of Japanese Patent Application No. 2003-176965 filed on June 20, 2003 which is the conventional priority case of the U.S. Patent Application No. 10/561,629.

Signature: ____________________
Seung-Lim SUNG

Date: **August 23, 2007**

[DOCUMENT TITLE] Patent Application
[REFERENCE NUMBER] 3562003JP
[FILING DATE] June 20, 2003
[TO] Commissioner of Patent Office
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A61K 47/38
A61P 27/02

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[PAID FEE] 21000 yen
[LIST OF THE FILED DOCUMENTS]
[DOCUMENT TITLE] SPECIFICATION 1
[DOCUMENT TITLE] ABSTRACT 1
[ID CODE ON GENERAL POWER OF ATTORNEY] 9709352
[PROOF] Necessary

[DOCUMENT TITLE] SPECIFICATION

[TITLE OF INVENTION] Ophthalmic Composition

[CLAIMS]

[CLAIM 1] An ophthalmic composition which comprises pyridoxine hydrochloride, chondroitin sulfate salt and cellulose based polymer compound.

[CLAIM 2] The ophthalmic composition according to claim 1 wherein said cellulose based polymer compound is at least one compound selected from hydroxyethyl cellulose, methyl cellulose, and hydroxypropyl methyl cellulose.

[CLAIM 3] A process for alleviating an irritation to eyes with an ophthalmic composition containing pyridoxine hydrochloride, the process comprises blending a chondroitin sulfate salt and cellulose based polymer compound together with an ophthalmic composition containing pyridoxine hydrochloride.

[CLAIM 4] The process for alleviating an irritation according to claim 3, wherein said cellulose based polymer compound is at least one compound selected from hydroxyethyl cellulose, methyl cellulose, and hydroxypropyl methyl cellulose.

[DETAILED DESCRIPTION OF THE INVENTION]

[0001]

[TECHNICAL FIELD WHERE THE INVENTION BELONGS]

The present invention relates to an ophthalmic composition. More particularly, of an ophthalmic composition containing pyridoxine hydrochloride, the present invention relates to the ophthalmic composition which exhibits the reduced irritation to eyes. Furthermore, the present invention relates to a process for alleviating irritation to eyes with an ophthalmic composition including pyridoxine hydrochloride.

[0002]

[PRIOR ART]

In the development of pharmaceutical products for use in the ophthalmologic field, irritations to the ophthalmic mucosa and discomfort have to be always considered in addition to the medical effect thereof. Hence, with regard to various types of

active components used in the conventional ophthalmic compositions, some processes for removing or alleviating and moderating the irritation have been proposed.

【0003】

For example, Patent Literature 1 discloses a process for moderating with cyclosporine irritations to mucosa of eyes, nose or the like due to cetirizine to be acted as an antiallergic agent; Patent Literature 2 discloses a process for moderating irritations to eyes with 2-(2-fluoro-4-biphenylyl)propionic acid which is used as an anti-inflammatory agent by blending one or two or more of polyvinyl alcohol, methyl cellulose, carboxymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl methyl cellulose and sodium chondroitin sulfate in an amount of 0.01 to 2% to form a composition with the pH 5-8 so adjusted; Patent Literatures 3 and 4 disclose a process for moderating irritations to eyes with 2-acetyl-1-(2-hydroxy-8-isopropylaminopropoxy)benzofuran which is used as an intraocular pressure decreasing agent or a therapeutic agent for glaucoma by blending (A) 0.001 to 0.1% benzalkonium chloride or benzethonium chloride, and (B) at least one compound of polyvinyl alcohol, methyl cellulose, carboxymethyl cellulose and hydroxyethyl cellulose in an amount of 0.02 to 2 w/v%, or hydroxypropyl methyl cellulose in an amount of 0.01 to 1 w/v% to form a composition with the pH 5-8 so adjusted; and, Patent Literature 5 disocloses a process for moderating irritations to eyes with lower alcohol such as ethanol which is used as a refrigerant by blending a saccharide such as mannitol, xylitol, glucose and maltose.

【0004】

Accordingly, various types of irritating components are available, and under current circumstances, processes for removing or alleviating and moderating the wide variety of different irritations have been studied and proposed depending on the type thereof.

【0005】

【Patent Literature 1】 Japanese Patent Provisional Publication No. 6-239748.

【0006】

【Patent Literature 2】 Japanese Patent Provisional Publication No. 57-102817.

【0007】

【Patent Literature 3】 Japanese Patent Provisional Publication No. 56-39013.

【0008】

【Patent Literature 4】 Japanese Patent Provisional Publication No. 57-16817.

【0009】

【Patent Literature 5】 Japanese Patent Provisional Publication No. 2001-261578.

【0010】

【PROBLEMS TO BE SOLVED BY THE INVENTION】

An object of the present invention is to provide a process for alleviating an irritation or discomfort to eyes with pyridoxine hydrochloride which has often been used in ophthalmic-pharmaceutical compositions to expect the moderating effects of asthenopia, and an ophthalmic composition which alleviates an irritation to eyes according to the process.

【0011】

【ELEMENTS TO SOLVE THE PROBLEMS】

The present inventor investigated to develop an ophthalmic composition to moderate asthenopia, and discovered that an ophthalmic composition containing pyridoxine hydrochloride as an active component to moderate asthenopia may cause an unpleasant irritation to the ophthalmic mucosa. Hence, as a consequence of elaborate investigations for eliminating such problems and for obtaining a desired ophthalmic composition as described above, it was found that preparation of an ophthalmic composition containing the combined components of chondroitin sulfate salt and cellulose based polymer compound, in addition to pyridoxine hydrochloride, enables an ophthalmic composition

to moderate asthenopia without unpleasant irritation through alleviating or removing irritation to be generated from pyridoxine hydrochloride. Furthermore, the effect of alleviating or removing the unpleasant irritation allows using a large amount of pyridoxine hydrochloride, thereby, an ophthalmic composition may then moderate asthenopia remarkably. The present invention was accomplished based on such investigation results.

【0012】

Accordingly, merits of the present invention are as follows.

Item 1. An ophthalmic composition which comprises pyridoxine hydrochloride, chondroitin sulfate salt and cellulose based polymer compound.

Item 2. The ophthalmic composition according to the item 1 wherein said cellulose based polymer compound is at least one compound selected from hydroxyethyl cellulose, methyl cellulose, and hydroxypropyl methyl cellulose.

Item 3. A process for alleviating an irritation to eyes with an ophthalmic composition containing pyridoxine hydrochloride, the process comprises blending chondroitin sulfate salt and cellulose based polymer compound together with an ophthalmic composition containing pyridoxine hydrochloride.

Item 4. The process for alleviating an irritation according to the item 3 wherein said cellulose based polymer compound is at least one compound selected from hydroxyethyl cellulose, methyl cellulose, and hydroxypropyl methyl cellulose.

【0013】

【EMBODIMENTS】

(1) Ophthalmic Composition

The ophthalmic composition of the present invention uses pyridoxine hydrochloride as an active component, and the combined components of chondroitin sulfate salt and cellulose based polymer allow to accompolish the merits of the present invention to provide an ophthalmic composition which can be used

without unacceptable sense and can offer an improved effect to moderate asthenopia due to pyridoxine hydrochloride, through alleviation or removal of the irritation resulting from the aforementioned pyridoxine hydrochloride.

【0014】

Chondroitin sulfate salt to be used in the present invention is not particularly limited as long as it is a pharmaceutically acceptable salt of chondroitin sulfate, but may be usually sodium chondroitin sulfate. An amount of the chondroitin sulfate salt to be blended into the ophthalmic composition is not particularly limited as long as the merit of the present invention is accomplished, but illustrative range thereof may be 0.001 w/v% or more, preferably 0.001 to 0.5 w/v%, and more preferably 0.005 to 0.5 w/v% in 100 w/v% of the ophthalmic composition. Also, exemplary ratio to pyridoxine hydrochloride to be blended into the ophthalmic composition may be 0.01 to 2,000 parts by weight, preferably 0.05 to 2,000 parts by weight, and more preferably 0.05 to 500 parts by weight per 1 part by weight of pyridoxine hydrochloride.

【0015】

Furthermore, specific examples of the cellulose based polymer compound which may be used in the present invention include alkyl cellulose such as methyl cellulose, ethyl cellulose and carboxymethyl cellulose; hydroxyalkyl cellulose such as hydroxyethyl cellulose, hydroxyethyl methyl cellulose, hydroxypropyl cellulose and hydroxypropyl methyl cellulose. Preferably, it may be methyl cellulose, hydroxypropyl methyl cellulose, or hydroxyethyl cellulose, and more preferably, methyl cellulose or hydroxypropyl methyl cellulose. These may be used alone, or in optional combination of two or more of them.

【0016】

An amount of the blended cellulose based polymer compound to be used in the ophthalmic composition is not particularly limited as long as the merit of the present invention is accomplished. In general, the amount thereof can not be determined regularly, because it may vary depending on the type

of the cellulose based polymer compound as actually used, but can be selected and adjusted ad libitum to fall within the range of 0.01 to 10 w/v%, preferably 0.01 to 5 w/v%, and more preferably 0.05 to 5 w/v% in 100 w/v% of the ophthalmic composition as a reference. Also, exemplary ratio to pyridoxine hydrochloride blended into the ophthalmic composition may be 0.1 to 10,000 parts by weight, preferably 0.1 to 5,000 parts by weight, and more preferably 0.1 to 200 parts by weight per 1 part by weight of pyridoxine hydrochloride. Moreover, it is desired to adjust the ratio of the cellulose based polymer compound per 1 part by weight of the chondroitin sulfate salt blended into the ophthalmic composition appropriately to be 0.02 to 10,000 parts by weight, preferably 0.02 to 5,000 parts by weight, and more preferably 0.02 to 1,000 parts by weight.

【0017】

The concentration of pyridoxine hydrochloride in the ophthalmic composition of the present invention may vary widely depending on the particular use of the composition (either pharmaceutical use or the other use) and extent of the asthenopia to be ameliorated, but may be usually 0.001 w/v% or more, preferably 0.001 to 1 w/v%, and more preferably 0.001 to 0.1 w/v%.

【0018】

The ophthalmic composition of the present invention is preferably adjusted to the pH range which is generally acceptable for ophthalmic applications. Specifically, pH may fall within the range of from 4 to 9, preferably 5 to 8, and more preferably 5.5 to 8.

【0019】

Furthermore, the ophthalmic composition of the present invention is preferably adjusted to the osmotic pressure range which is generally acceptable for ophthalmic applications. Specifically, it is preferably adjusted to be a pressure ratio falling within the range of 0.5 to 5, and more preferably within the range of the pressure ratio of 0.8 to 2. For adjusting the osmotic pressure, for example, any method usually adopted in

preparation of eye drops can be used in a similar manner.

【0020】

Besides pyridoxine hydrochloride, any component to be acted to moderate asthenopia may be blended in the ophthalmic composition of the present invention as long as the merit of the present invention is not impaired. Also, other pharmaceutically effective components commonly used in ophthalmologic field may also be blended ad libitum.

【0021】

Such pharmaceutically effective components are not limited, and illustrative examples thereof include decongestants (e.g., naphazoline hydrochloride, tetrahydrozoline hydrochloride, phenylephrine hydrochloride, epinephrine hydrochloride and the like), antiphlogistic, astringent drugs (e.g., neostigmine methylsulfate, ε-amino caproic acid, allantoin, berberine chloride, zinc sulfate, lysozyme chloride, sodium azulene sulfonate, dipotassium glycyrrhizinate and the like), antiallergic agents (diphenhydramine hydrochloride, isopenzyl hydrochloride, chlorpheniramine maleate, sodium cromoglycate and the like), vitamins other than pyridoxine hydrochloride (e.g., vitamin B_2, vitamin B_{12}, vitamin A, vitamin E, calcium pantothenate and the like), amino acids (potassium L-aspartate, magnesium L-aspartate, aminoethylsulfonic acid and the like), sulfa drugs (e.g., sulfamethoxazole, sulfisoxazole, sulfisomidine and the like), bacteriocides (sulfur, isopropylmethyl phenol, hinokithiol and the like), topical anesthetics (lidocaine, lidocaine hydrochloride, procaine hydrochloride, dibucaine hydrochloride and the like), inorganic salts (e.g., potassium chloride, sodium chloride, sodium bicarbonate and the like), thickening agents (polyvinyl alcohol, polyvinyl pyrrolidone, carboxymethyl cellulose, hyaluronic acid, glucose and the like), but not limited thereto.

【0022】

A variety of additives (e.g., solubilization auxiliary agents, isotonizing agents, stabilizing agents, chelating

agents, pH adjusting agents, refrigerants, preservatives, and thickening agents) as well as a carrier (e.g., buffer agents, and ointment bases) which may be generally used in ophthalmic compositions can also be blended, in addition to the aforementioned essential components, into the ophthalmic composition of the present invention in the range not to compromise the merit of the present invention.

【0023】

Illustrative examples of the solubilization auxiliary agent include polyethylene glycol, propylene glycol and the like; tonicity agent include sodium chloride, potassium chloride, sorbitol, mannitol, glycerin and the like; stabilizing agent include sodium edetate, cyclodextrin, sulfite, citric acid or salts thereof, and the like; the chelating agent include sodium edetate, sodium citrate and the like; pH adjusting agent include hydrochloric acid, citric acid or salts thereof, boric acid or salts thereof, phosphoric acid or salts thereof, acetic acid or salts thereof, tartaric acid or salts thereof, sodium hydroxide or potassium hydroxide, and the like; refrigerant include monoterpenoid compounds such as menthol, camphor, borneol, geraniol, cineol, limonene and eugenol, or peppermint oil, bergamot oil, eucalyptus oil, fennel oil, cool mint, and the like; examples of the preservative include paraoxybenzoic acid esters, benzalkonium chloride, chlorobutanol and the like; and moreover, thickening agent include polyvinyl alcohol, polyvinylpyrrolidone, carboxymethyl cellulose, hyaluronic acid, glucose and the like.

【0024】

Furthermore, illustrative examples of the buffer agent include phosphoric acid or salts thereof (e.g., sodium monohydrogen phosphate and the like), boric acid or salts thereof (e.g., borax and the like), citric acid or salts thereof (e.g., sodium citrate and the like), tartaric acid or salts thereof (e.g., sodium tartrate and the like), gluconic acid or salts thereof (e.g., sodium gluconate and the like), acetic acid or salts thereof (e.g., sodium acetate and the like), various amino

acids, and the like.

【0025】

Moreover, illustrative examples of the base for use in the ophthalmic ointment include, for example, white petrolatum, liquid paraffin, carboxymethyl cellulose, macrogol, carboxyvinyl polymer, and the like.

【0026】

These compositions can be of any formulation generally used in ophthalmic compositions. Examples of such formulation include, for example, aqueous solutions, suspensions, emulsions, gelatinous materials, ointments and the like. Also, the dosage form is not particularly limited, but any form such as eye drops (including those for contact lenses), ophthalmic ointments, or eye lotions may be permitted. Furthermore, a solid type formulation prepared before use may be permitted which is obtained by solidifying the composition of the present invention by a process such as freeze-drying followed by forming a solid formulation like powder, granule or tablet form to be used after dissolution or the like in purified water upon use.

【0027】

The process for preparing the ophthalmic composition of the present invention is not particularly limited, but may be prepared according to common procedures for ophthalmic compositions. For example, the composition can be prepared by dissolving each component described above in water such as sterile purified water or ion exchanged water, or in a mixed solvent of the water and a lower alcohol such as ethanol, and thereafter, pH or osmotic pressure of the composition is adjusted appropriately with a pH adjusting agent, an isotonizing agent or the like.

【0028】

Preferrably, the ophthalmic composition of the present invention is administered, for example, into an adult in the form of an eye drops by dropping to eye one to few drop(s) per once approximately 3 to 6 times per day.

【0029】

[EFFECTS OF THE INVENTION]

The ophthalmic composition of the present invention has an effect to moderate asthenopia by pyridoxine hydrochloride used as an active component thereof, and an irritation to eyes with pyridoxine hydrochloride is also alleviated or removed by the combined components of chondroitin sulfate salt and cellulose based polymer compound. Therefore, according to the present invention, an ophthalmic composition can be used without unacceptable sense, and an effect to moderate asthenopia can be offered. Moreover, according to the present invention, a process for removing or alleviating an irritation to eyes with pyridoxine hydrochloride can be provided.

【0030】

[EXAMPLES]

Hereinafter, the present invention will be illustrated in detail by way of Example and Relative, but the present invention is not limited anyhow by the disclosure thereof.

【0031】

Examples 1-2, Relatives 1-6 and Control

Eye drops made from the prescription shown in Table 1 were prepared (Examples 1-2, Relatives 1-6, Control), and evaluated on the irritation when they were dropped in eyes. The viscosity of the eye drops is indicated as a value determined with B type viscometer at 20°C.

【0032】

Irritation to eyes was evaluated with sensory test wherein ten persons of adult men and women were participated. Each person rated irritation according to the following standard for eye drops of each prescription and evaluated it on the basis of the total points.

【0033】

<Evaluation on Moderation of Irritation>

No irritation experienced at all;	10 points
Irritation not experienced well;	5 points
Undecidable;	0 point
Irritation somewhat experienced;	-5 points
Irritation experienced;	-10 points

【0034】

The results are also shown in Table 1.

【0035】

[Table 1]

Amount blended (mg/100 mL)

	Example 1	Example 2	Relative 1	Relative 2	Relative 3	Relative 4	Relative 5	Relative 6	Control
Pyridoxine Hydrochloride	50	50	50	50	50	50	50	50	50
HPMC	300	-	300	-	300	500	-	300	-
Methyl Cellulose	-	300	-	-	500	-	-	100	-
Sodium Chondroitin Sulfate	500	500	-	500	-	-	800	-	-
Chlorpheniramine Maleate	15	15	15	15	15	15	15	15	15
Boric Acid	600	600	600	600	600	600	600	600	600
Glycerin	1750	1750	1750	1750	1750	1750	1750	1750	1750
Benzalkonium Hydrochloride	2	2	2	2	2	2	2	2	2
Disodium Edetate	5	5	5	5	5	5	5	5	5
Polysorbate 80	10	10	10	10	10	10	10	10	10
Sodium Hydroxide (pH adjusting agent)	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.
pH	5.7	5.7	5.7	5.7	5.7	5.7	5.7	5.7	5.7
Viscosity (cP)	11.1	10.2	8.67	1.81	124	25.6	2.28	14.0	1.16
Irritation to Eyes	100	80	-60	-60	-45	-55	-55	-40	-70

【0036】

In the Table, "HPMC" means hydroxypropyl methyl cellulose. As shown in Table 1, irritation to eyes with pyridoxine hydrochloride (Control) was revealed to be markedly alleviated or removed by using the combined components of the cellulose based polymer compound and sodium chondroitin sulfate (Examples 1 and 2). Furthermore, this effect was not exerted unless both the cellulose based polymer compound and sodium chondroitin sulfate were used, while the cellulose based polymer compound alone (Relatives 1 and 4) or combination thereof (Relatives 3 and 6), and sodium chondroitin sulfate alone (Relatives 2 and 5) exhibited no effect at all. Moreover, from the results of Relatives 1 and 4, Relatives 2 and 5, and Relatives 3 and 6 shown in Table 1, it was elucidated that the viscosity of the ophthalmic composition does not affect the moderation of irritation to eyes with pyridoxine hydrochloride.

【0037】

Example 3

An ophthalmic composition in the form of ointment was prepared according to the following prescription.

【0038】

Pyridoxine Hydrochloride	100 mg
HPMC	500
Sodium Chondroitin Sulfate	500
Sodium Cromoglycate	1,000
Carboxymethyl Cellulose	4,000
Glycerin	2,660
Benzalkonium Chloride	5
Polysorbate 80	20
Sodium hydroxide	q.s. (pH 5.7)
Sterile Purified Water	Residual amount
Total	100 mL

【0039】

Example 4

An ophthalmic solution was prepared according to the following prescription.

【0040】

Pyridoxine Hydrochloride	5 mg
HPMC	1,000
Sodium Chondroitin Sulfate	50
Disodium Glycyrrhizinate	5
Boric Acid	1,000
Benzalkonium Chloride	5
Disodium Edetate	5
Polysorbate 80	20
Sodium Hydroxide	q.s. (pH 5.7)
Sterile Purified Water	Residual amount
Total	100 mL

【0041】

Example 5

An eye drop was prepared according to the following prescription.

【0042】

Pyridoxine Hydrochloride	50 mg
HPMC	300
Sodium Chondroitin Sulfate	500
Chlorpheniramine Maleate	15
Boric Acid	600
Glycerin	1,750
Benzalkonium Chloride	2
Disodium Edetate	5
Polysorbate 80	10
Sodium Hydroxide	q.s. (pH 5.7)
Sterile Purified Water	Residual amount
Total	100 mL

[DOCUMENT TITLE] ABSTRACT

[ABSTRACT]

[PROBLEM] To provide an ophthalmic compositions which alleviate or remove eye irritation due to the pyridoxine hydrochloride even though the composition comprises pyridoxine hydrochloride as an essential element.

[MEAN TO SOLVE] In the preparation of an ophthalmic composition, chondroitin sulfate salt and cellulose based polymer compound are used in combination with pyridoxine hydrochloride.

[REPRESENTATIVE FIGURE] None

APPENDIX 5

Docket No.: 19036/40796
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Yuka Matsui

Application No.: 10/561,629 — Confirmation No.: 8420

Filed: June 21, 2004 as PCT/JP2004/008710 (national stage entry on December 20, 2005) — Art Unit: Not Yet Assigned

For: OPHTHALMIC COMPOSITION — Examiner: Not Yet Assigned

DECLARATION OF FACTS FOR PETITION TO ACCEPT FILING UNDER 37 CFR §1.47(b)

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I, Naonori Murakami, hereby declare as follows:

1. I am currently Director of Corporate Brand Planning Division of Kobayashi Pharmaceutical Company, Ltd. I submit this Declaration to provide facts to the United States Patent and Trademark Office relating to Kobayashi Pharmaceutical's proprietary interest in the above-identified patent application, naming Yuka Matsui as sole inventor.

2. I was Director at the Research and Development Company of Kobayashi Pharmaceutical Co., Ltd, in June 2003, when the priority document, Japanese Application No. 2003-176965, for the above-identified application was filed. My duties as Director included ensuring transfer of ownership of subject matter in patent applications from the inventor(s) to Kobayashi Pharmaceutical. I was also responsible for ensuring that inventors executed a "Regulation for Employee's Invention Management." All employees at Kobayashi Pharmaceutical are obliged to execute this oath, which provides that an employer has the right to obtain a patent on any employee invention. A copy of an executed oath by

Ms. Matsui on April 16, 2001, wherein she promises to observe the working regulations of Kobayashi, is attached as Exhibit A to this declaration. The working regulations include those associated with employees' inventions. An English translation of the oath executed by Ms. Matsui and of the relevant portions of the working regulations (Regulations for Employee's Invention) are attached as Exhibits B and C, respectively, to this declaration.

3. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. §1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Dated: September 28, 2007

Signed: N. Murakami

Name: Naonori Murakami

EXHIBIT A

JAPANESE LANGUAGE
ORIGINAL WRITTEN OATH

平成 13 年 4 月 16 日

小林製薬株式会社 御中

住　　所：茨木市西中条1-22エンゼルハイタウン301号

従業員コード：[redacted]

氏　　名：松中優香 (印)

誓　約　書

私は貴社に在籍するに際し、以下の事項を遵守することを誓約いたします。

1．貴社の就業規則および服務に関する諸規程を遵守し、誠実に職務を尽くすこと。

2．貴社の企業秘密を、在職中はもちろん退職後も、貴社の許可なく第三者に開示もしくは漏洩しないこと。

3．貴社の企業秘密を、在職中はもちろん退職後3年間も、自己のため、または貴社と競業する事業者その他第三者のために、使用しないこと。

（企業秘密とは、不正競争防止法2条4項「営業秘密」を含む。）

以　上

EXHIBIT B

PATENT CORPORATE BODY
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

U.S. Patent Application No. 10/561,629
(U.S. National Phase of PCT/JP2004/008710)
Of Yuka MATSUI (KOBAYASHI PHARMACEUTICAL CO., LTD.)

I, **Seung-Lim SUNG**, of ARCO PATENT OFFICE at 3rd Fl., Bo-eki Building, 123 Higashi-machi, Chuo-ku, Kobe 650-0031 JAPAN, declare that I am familiar with the Japanese and the English languages, and, to the best of my knowledge and belief, the attached are:

(1) full, true, complete and faithful my prepared English translation of WRITTEN OATH by Ms. Yuka MATSUI executed on April 16, 2001 (Exhibit B);

(2) full, true, complete and faithful my prepared English translation of REGULATIONS FOR EMPLOYEE'S INVENTION in KOBAYASHI PHARMACEUTICAL CO. LTD. (Exhibit C); and

(3) a copy of the original Japanese REGULATIONS FOR EMPLOYEE'S INVENTION subjected for the English translation identified as Exhibit C above.

Signature: _____
Seung-Lim SUNG

Date: **October 4, 2007**

April 16, 2001

TO: KOBAYASHI PHARMACEUTICAL CO, LTD.

ADDRESS: Angel Uchida #301,
1-22 Nishichujo, Ibaraki-shi
EMPLOYEE ID: [redacted]
NAME: **Yuka MATSUI** [signature][seal]

WRITTEN OATH

I swear an oath to observe the following matters at the entering into KOBAYASHI PHARMACEUTICAL CO, LTD.(KOBAYASHI).

1. To observe the working regulations and any other regulation on duty respectively provided by KOBAYASHI and to sincerely perform my own duty work.

2. Not to disclose or leak any corporate secret of KOBAYASHI to any third party without permission of KOBAYASHI over my tenure as well as after my retirement.

3. Not to use any corporate secret of KOBAYASHI for myself or for the third party including a legal entity which competes to KOBAYASHI over my tenure as well as within three years from my retirement.

(The term 'corporate secret' used herein may include "trade secret" according to Unfair Competition Prevention Act Article 2(4).)

Respectfully submitted.

EXHIBIT C

JAPANESE LANGUAGE
ORIGINAL REGURATION

職 務 発 明 規 程

(研究開発カンパニー編)

第１条（規程の目的）

この規程は、小林製薬株式会社の従業員に発明研究を奨励し、従業員がなした発明について権利の帰属を明らかにし、その発明者としての権利を保障することにより、社業の発展に寄与することを目的とするものである。

第２条（用語の定義）

「職務発明」とは、発明がその性質上会社の業務範囲に属し、かつ、その発明をするにいたった行為が会社における従業員の現在または過去の職務に属する発明をいう。

第３条（権利の帰属）

会社は、従業員がなした職務発明について、特許を受ける権利または特許権を承継することができる。

２.従業員が社外の個人、または団体と共同して職務発明をしたときは、その従業員の発明に関する持分の承継は前項の規程によるものとする。

第４条（届出）

発明をした従業員は、すみやかにその発明の内容を自己の所属する長に届け出なければならない。

２.所属の長は、前項の規程による届出をうけたときは、当該届出にかかわる内容に権利の帰属等に関する意見書を添えて会社に提出しなければならない。

第５条（職務発明の認定および承継の決定）

会社は、前条第２項の規程による届出があったときは、当該届出にかかわる発明が職務発明であるかどうかの認定をし、職務発明であると認定したときは、当該発明について特許を受ける権利を会社が承継するかどうかの決定をするものとする。

２.会社は、前項の規程により認定および決定したときは、速やかにその旨を発明者に所属の長を経由して、文書で通知しなければならない。

第６条（個人出願および第三者への権利の譲渡に対する制限）

発明者は、会社が前条１項により、職務発明でないと認定し、または会社で承継しないと決定したあとでなければ、特許出願をし、または特許を受ける権利を第三者に譲渡してはならない。

２.発明者は、特許を受ける権利を他に譲渡した場合、これを会社に通知しなければならない。

第７条（出願手続）

会社は、第５条第１項の規程により特許を受ける権利を承継すると決定した職務発明については、速やかに出願手続をとり、その処分の確定に至るまでに生ずる必要手続をその都度行うものとする。

第８条（特許を受ける権利の譲渡義務）

発明者は、会社が第５条第１項の規程により、当該発明者の発明について、特許を受ける権利を会社が承継すると決定をしたときは、その権利を会社に譲渡しなければならない。

第９条（異議の申立および再認定の通知）

発明者は、第５条第１項の認定に対し会社に異議の申立てをすることができる。

２.会社は前項の異議の申立てにつき、職務発明であると再認し、またはその他の発明であると異議を認めたときは理由を附して当該発明者に通知するものとする。

第１０条（実施権）

会社は、第５条第１項の規程により特許を受ける権利を承継しないと決定した職務発明について、発明者またはその承継人が特許権を取得した場合は、当該職務発明について実施権を有する。

第１１条（補償金の支払い）

会社は、会社が次の各号に掲げる場合において特許を受ける権利または特許権を取得したときは、当該特許権にかかわる発明をした発明者に対し、別に定める補償金を支払うものとする。

（１）会社が特許を受ける権利を承継し、これを特許出願したとき。

（２）会社が特許を受ける権利を承継し、これが登録になったとき。

（３）会社が特許権を譲り受けたとき。

第１２条（共同発明者に対する補償）

前条の補償金は、当該補償金を受ける権利を有する発明者が２人以上あるときは、それぞれの持分に応じて支払うものとする。 ただし、１０円未満の端数は切り上げるものとする。

第１３条（転退職または死亡したときの補償）

第１１条の補償金を受ける権利は、当該権利にかかわる発明者が転職し、または退職した後も存続する。

２.前項の権利を有する発明者が死亡したときは、当該権利は、その相続人が承継する。

第１４条（発明審査事務局の設置）

この規程を実施するため、発明審査事務局を置き、その事務は研究開発管理部においてつかさどる。

第１５条（異議の申立）

発明者は、その発明にかかわる第５条第１項の通知を受けた日から３ヶ月以内に会社に対し、文書をもって、異議の申立てをすることができる。

２.会社は、前項の申立てを受けたときは、事実の決定を行い、その結果を申立人に対し、異議申立て日より３ヶ月以内に通知しなければならない。

第１６条（秘密の保持）

発明者および発明審査事務局の関係者は、発明の内容その他、発明者および会社の利害に関係ある事項について必要な期間中その秘密を守らなければならない。

第１７条（職務発明でない発明）

会社は、第５条第１項の規程により、職務発明でないと認定した発明について、発明者から特許を受ける権利または特許権を譲渡したい旨の申出があったときは、特許を受ける権利または特許権を承継することができる。

２.前項の場合の取り扱いは、職務発明の取り扱いに準ずる。

第１８条（嘱託および臨時雇の取扱い）

常勤嘱託、または臨時雇がその職務に関してなした発明については、それが嘱託または臨時に従事する職務に関係するものは従業員の発明とみなして本規程を適用する。

２.非常勤の嘱託または顧問が会社の業務に関係ある発明をなした場合、会社が必要と認めたときは、本人の承諾を得て本規程を適用する。

第１９条（実用新案権　意匠権に関する準用）

この規程は、実用新案権及び意匠権の取扱いについて準用する。

第２０条（外国出願の取扱い）

この規程は、外国の工業所有権を対象とする発明に関してもこれを準用する。

第２１条（準拠）

この規程に定めのない事項は、関係法令及び他の社内規程、規準の定めによるほか発明審査事務局の所属長の指示によるものとする。

附　則

１.この規程の改廃は、規程管理規程別紙の審査機関に諮問したうえで決定機関にて承認を得ることとする。

２.この規程は、平成７年１０月１日出願分より施行する。

３.この規程は、施行日以前の出願には適用しない。

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REGULATIONS FOR EMPLOYEE'S INVENTION
(EDITED BY RESEARCH & DEVELOPMENT COMPANY)

(PURPOSE OF REGULATIONS)

1. This regulation aims to encourage the employees of KOBAYASHI PHARMACEUTICAL CO, LTD. (the employer) to persevere in research and complete an invention, to clarify ownership of the achieved invention, to secure the rights as an inventor, and to ultimately contribute thereby to the development of the employer's business.

(DEFINITION OF TERM)

2. 'EMPLOYEE'S INVENTION' means an invention which, by its nature, falls within the scope of the business of the employer and was achieved by an act or acts categorized as a present or past duty of the employees performed on behalf of the employer.

(OWNERSHIP OF INVENTION)

3.(1) The employer may succeed to the right to obtain a patent or the patent right with respect to EMPLOYEE'S INVENTION achieved by the employees.

(2) In case the employees achieved EMPLOYEE'S INVENTION in cooperation with an outside individual or an outside legal entity, the employer succeeds to the employee's own share pursuant to Article 3(1).

(NOTIFICATION)

4.(1) The employees who achieved an invention shall have rapidly notified merit of the invention to the director who supervises the inventor.

(2) The director who received the notification pursuant to Article 4(1) shall have notified the employer the reported matter together with comment on ownership of the right.

(JUDGMENT REGARDING EMPLOYEE'S INVENTION AND INHERITANCE)

5.(1) Upon receiving the notification pursuant to Article 4 (2), the employer shall judge as to whether or not that the notified invention is EMPLOYEE'S INVENTION, then in case the employer judges the notified invention as EMPLOYEE'S INVENTION, the employer shall further decide as to whether or not that the employer succeeds to the right to obtain a patent with respect to EMPLOYEE'S INVENTION.

(2) In case the judgment and decision are made pursuant to Article 5 (1), the employer shall have rapidly provided a written notice on such judgment and decision to the inventor through the director who supervises the inventor.

(RESTRICTION TO FILE PATENT APPLICATION BY THE INVENTOR AND TO ASSIGN ANY RIGHT THEREON TO THE THIRD PARTY)

6.(1) In case any judgment by the employer as EMPLOYEE'S INVENTION or any decision to succeed EMPLOYEE'S INVENTION to the employer is not made yet pursuant to Article 5 (1), the inventor shall not file any patent application or shall not assign any right thereon to the third party.

(2) In case the right to obtain a patent is assigned to the others, the inventor shall have notified such assignment to the employer.

(FILING OF PATENT APPLICATION)

7. The employer shall rapidly file a patent application with respect to EMPLOYEE'S INVENTION decided pursuant to Article 5 (1) to succeed to the employer to the right to obtain a patent, and take necessary steps after the filing of the patent application until the conclusive examination result thereof is drawn.

(DUTY TO ASSIGN THE RIGHT TO OBTAIN A PATENT)

8. When the employer decides pursuant to Article 5 (1) to succeed to the employer to the right to obtain a patent with respect to an invention by the inventor, the inventor shall have assigned the right to the employer.

(OPPOSITION AND NOTIFICATION OF REEXAMINATION)

9.(1) The inventor may raise an opposition against the employer with respect to the judgment pursuant to Article 5 (1).

(2) In case the employer reconfirms the invention as EMPLOYEE'S INVENTION in response to the opposition pursuant to Article 9 (1), or accepts the opposition and regards it as non-EMPLOYEE'S INVENTION, the employer shall notify the examination result to the inventor together with the grounds.

(LICENSE)

10. In case the inventor or his/her successor is granted a patent right with respect to EMPLOYEE'S INVENTION decided not to succeed to the employer to the right to obtain a patent thereon pursuant to Article 5 (1), the employer has a license on such EMPLOYEE'S INVENTION.

(PAYMENT OF COMPENSATION)

11. In case the employer takes the right to obtain a patent or the patent right under the condition fallen within any of the following paragraphs, the employer shall pay compensation pursuant to the rule prescribed separately to the inventor who achieved the invention involved with such patent right.

(1) The employer succeeded to the right to obtain a patent and files a patent application thereof.

(2) The employer succeeded to the right to obtain a patent and a patent is granted thereon.

(3) The patent right was assigned to the employer.

(COMPENSATION FOR JOINT INVENTORS)

12. In case two or more inventors take the right to receive the compensation pursuant to Article 11, the compensation shall be paid according to each inventor's own share. Fraction less than ten (10) yen is however rounded up.

(COMPENSATION FOR INVENTOR WHO HAS LEFT, RETIRED OR DECEASED)

13.(1) The right to receive compensation pursuant to Article 11 shall remain even after the inventor has left or retired.

(2) In case the inventor who had the right pursuant to Article 13 (1) and has deceased, his/her heir inherits the right.

(ORGANIZATION OF EXAMINATION OFFICE ON INVENTION)

14. In order to enforce this regulation, Examination Office on Invention is organized and clerical work thereof shall be attended in Management Department of Research & Development.

(OPPOSITION)

15.(1) The inventor may raise an opposition in a written form against the employer within three months from the receiving date of the notification pursuant to Article 5 (1) with respect to the invention subjected therein.

(2) In case the employer accepts an opposition pursuant to Article 15 (1), the employer shall decide fact of the matter and shall notify the result thereof within three months from the filing date of the opposition.

(OBLIGATION OF CONFIDENTIALITY)

16. The inventor and persons whom it may concern with Examination Office on Invention shall have maintained, during the necessary period, the secrecy about the merit of the invention, the other matters on the invention, and any matter to be concerned with the inventor and the employer.

(NON-EMPLOYEE'S INVENTION)

17.(1) In case the inventor offers assignment of the right to obtain a patent or a patent right with respect to an invention not judged as EMPLOYEE'S INVENTION pursuant to Article 5 (1), the employer may succeed to the right to obtain a patent or the patent right.

(2) Handling of EMPLOYEE'S INVENTION applies mutatis mutandis to the handling of the case pursuant to Article 17 (1).

(HANDLING OF TEMPORARY EMPLOYEES AND TRANSIENT EMPLOYEES)

18.(1) An invention achieved by full-time temporary employees or transient employees and concerned with the business where temporary or transiently engaged shall be regarded as the invention by the employees and is subjected to this regulation.

(2) In case part-time temporary employees or corporate adviser achieved an invention concerned with the business of the employer, upon acknowledging the necessity by the employer, this regulation shall apply thereto with consent of the person.

(APPLICABILITY TO UTILITY MODEL RIGHT AND DESIGN RIGHT)

19. This regulation applies mutatis mutandis to the handling of utility model right and design right.

(HANDLING OF FOREIGN APPLICATION)

20. This regulation applies mutatis mutandis to the invention to be subjected for foreign industrial properties.

(COMPLIANCE)

21. Any matter not stipulated in this regulation shall be settled upon relevant laws and regulations, in house regulations and criteria, otherwise, instruction by the director who supervises Examination Office on Invention.

Supplementary Provision

1. Improvement or elimination of this regulation shall firstly consult Council listed in Appendix of Regulation for Managing Regulation and then secure authoritative approval.

2. This regulation shall be effective for an invention that has filed on October 1, 1995 or later.

3. This regulation shall not be effective for any invention that has filed on or before September 30, 1995.

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